BRIEF ARTICLE

Efficacy evaluation of imatinib treatment in patients with gastrointestinal stromal tumors: A meta-analysis

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Abstract

AIM: To perform a meta-analysis to derive a more precise estimation of imatinib treatment for different genotypes of gastrointestinal stromal tumors (GIST).

METHODS: Studies were identified by searching PubMed and Embase. Inclusive criteria were patients with exon 9-mutant, exon 11-mutant or wide type (WT) GIST, receiving chemotherapy of imatinib for clinical trial, and efficacy evaluation was cumulative response (CR) including complete response and partial response. The odds ratios (OR) for CR in stem cell factor receptor (KIT) mutation patients *vs* WT genotype patients, KIT exon 11-mutant genotype patients *vs* KIT exon 9-mutant genotype patients and KIT exon 9-mutant genotype patients *vs* WT genotype patients were calculated with 95% confidence interval (CI) for each study as an estimation of the efficacy of imatinib.

RESULTS: Five studies including 927 patients were involved in this meta-analysis. The overall OR (KIT group *vs* WT group) was 3.34 (95% CI: 2.30-4.86, P < 0.00001, $P_{heterogeneity}$ = 0.04). The overall OR in KIT exon 11 group *vs* KIT exon 9 group was 3.29 (95% CI: 2.17-5.00, P < 0.00001, $P_{heterogeneity}$ = 0.33). The overall

OR in KIT exon 9 group *vs* WT group was 1.23 (95% CI: 0.73-2.10, P = 0.44, $P_{heterogeneity}$ = 0.42).

CONCLUSION: Most patients with different genotypes of GIST and KIT exon 11-mutant will benefit from the individualized treatment of imatinib.

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a rare tumor, but the most common mesenchymal malignancy of the gastrointestinal tract[1]. GIST expresses the tyrosine kinase receptor KIT, which is the protein product of the KIT proto-oncogene. GIST is generally characterized by gain-of-function mutations of KIT[2]. These mutations result in the constitutive activation of KIT signaling and are the likely causal molecular events of GIST[3,4]. No effective systemic treatment is available. Imatinib (STI571) inhibits a similar tyrosine kinase, BCR-ABL, leading to responses in chronic myeloid leukemia, and has also been shown to inhibit KIT.

Imatinib, an active tyrosine kinase inhibitor against

KIT and platelet-derived growth factor receptor, has been shown to be highly effective in the treatment of advanced GIST. Clinical benefit was demonstrated in more than 80% of patients, resulting in a substantial improvement in the 2-year survival rate from 26% to 76%[5,6]. Imatinib has, therefore, become the standard of care in patients with advanced GIST. However, secondary resistance to imatinib often occurs within the first or second year of treatment[7], which indicated the need for differential treatment of patients with GIST. According to the previous reports, laboratory studies revealed significant molecular heterogeneity among GIST. Notably, 75%-85% of GIST had an activating mutation of KIT, 5%-7% had an activating mutation of the homologous PDGFRA kinase, and approximately 12%-15% of GIST did not have a detectable mutation of either Kinase[8-10]. And several studies have been designed to test the sensitivity of imatinib to different genotypes of GIST. Therefore, we made a meta-analysis of response to different genotypes to identify which one is more sensitive to imatinib.

MATERIALS AND METHODS

Publication search
Two electronic databases (PubMed and Embase) were searched (the last search was done on January 1, 2010, using the terms: "gastrointestinal stromal tumor" and "imatinib"). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Only published studies with full-text articles were included. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

Inclusion criteria
The inclusion criteria were as follows: (1) assessing the efficacy of imatinib in treatment of patients with different genotypes of GIST; (2) clinical trial studies; and (3) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI).

Data extraction
Information was carefully extracted from all eligible studies. The following data were collected from each study: first author's surname, publication date, treatment protocols and total number of KIT mutation cases, KIT exon 11 cases, KIT exon 9 cases and WT cases, and numbers of KIT mutation cases, KIT exon 11 cases, KIT exon 9 cases and wild type (WT) cases, with the clinical CR after the treatment of imatinib, respectively. We did not define any minimum number limit of patients to include a study in our meta-analysis.

Statistical analysis
Odd ratios with 95% CI were used to assess the efficacy of imatinib in treatment of patients with different genotypes of GIST according to the method of Woolf. Heterogeneity assumption was checked by the χ^2-based

Q test. $P > 0.10$ for the Q test indicates a lack of heterogeneity among studies, so the OR estimate of each study was calculated by the fixed-effects model (the Mantel-Haenszel method). Otherwise, the random-effects model (the DerSimonian and Laird method) was used. The significance of the pooled OR was determined by the Z test and $P > 0.05$ was considered as statistically significant. Sensitivity analyses were carried out to check if modification of the inclusion criteria of this meta-analysis affected the final results. Potential publication bias was estimated by the funnel plot, in which the OR of each study was plotted against its log. An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, and funnel plot asymmetry on the natural logarithm scale of the OR was measured by a linear regression approach. The significance of the intercept was determined by t test ($P < 0.05$ was representative of statistically significant publication bias). All the statistical tests were performed with Review Manager Version 4.2 (The Cochrane Collaboration, Oxford, England) and STATA version 9.2 (Stata Corporation, College Station, TX, USA).
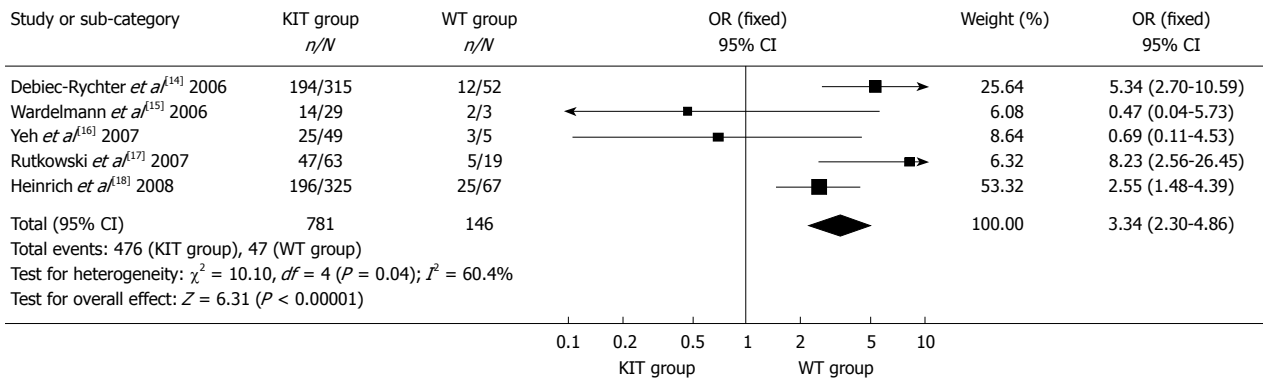
RESULTS

Study characteristics
Five publications met the inclusion criteria. The study by Blanke *et al*[11] was excluded due to the fact that it only revealed the prognostic factor and so did the study by Tzen *et al*[12]. Likewise, the study by Andersson *et al*[13] was excluded because the study was designed for a random, double-blind, 400 mg *vs* 600 mg imatinib controlled trial only used to prove the effective dosage to treat GIST. Hence, five groups including 927 patients were used in the pooled analyses. Table 1 lists the studies identified and their main characteristics. Of the five groups, sample sizes ranged from 32 to 392. Almost all of the patients with GIST were confirmed by histology and immunohistochemistry, and DNA sequence was identified by polymerase chain reaction technique. No significant differences were found in the age distributions and sex difference among all the studies.

Meta-analysis results
Overall meta-analysis indicated that the cumulative response of KIT mutation group to imatinib was significantly different compared with that of WT group (OR 3.34, 95% CI: 2.30-4.86; $P < 0.00001$, $P_{heterogeneity} = 0.04$) (Figure 1A). A significant heterogeneity was found by simply comparing those five combined samples ($P < 0.10$). The overall OR for KIT exon 11 group *vs* KIT exon 9 group and KIT exon 9 group *vs* WT group were 3.29 (95% CI: 2.17-5.00, $P < 0.00001$, $P_{heterogeneity} = 0.33$) and 1.23 (95% CI: 0.73-2.10, $P = 0.44$ $P_{heterogeneity} = 0.42$), respectively (Figure 1B and C). Although the CR in the study of Wardelmann *et al*[15] and Yeh *et al*[16] did not follow the tendency of other studies, the corresponding pooled OR was not materially altered with or without these two studies. No other single study influenced the pooled OR qualitatively as indicated by sensitivity analyses (data not shown).
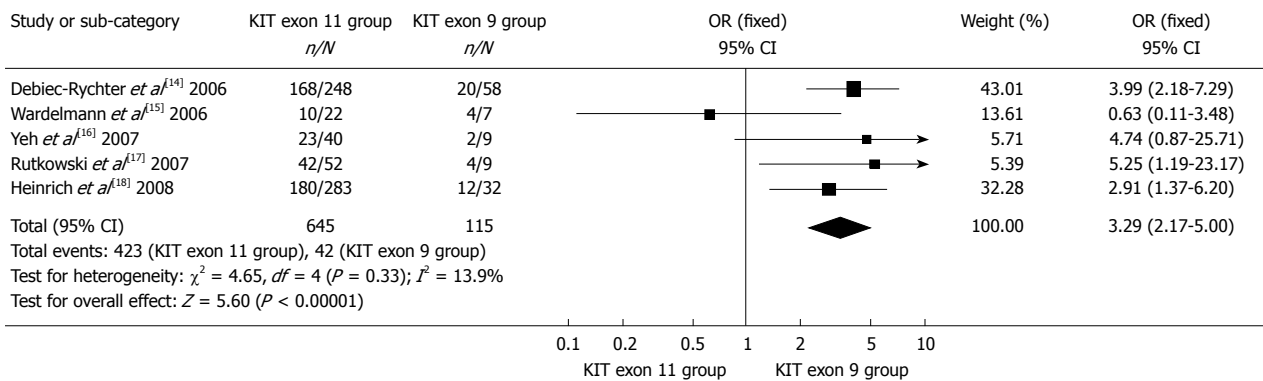
A

Review:	Efficacy evaluation of imatinib therapy in patients with gastrointestinal stromal tumors: A meta-analysis				
Comparison:	01 KIT group *vs* WT group				
Outcome:	01 cumulative response to imatinib				

Study or sub-category	KIT group *n/N*	WT group *n/N*	OR (fixed) 95% CI	Weight (%)	OR (fixed) 95% CI
Debiec-Rychter *et al*[14] 2006	194/315	12/52		25.64	5.34 (2.70-10.59)
Wardelmann *et al*[15] 2006	14/29	2/3		6.08	0.47 (0.04-5.73)
Yeh *et al*[16] 2007	25/49	3/5		8.64	0.69 (0.11-4.53)
Rutkowski *et al*[17] 2007	47/63	5/19		6.32	8.23 (2.56-26.45)
Heinrich *et al*[18] 2008	196/325	25/67		53.32	2.55 (1.48-4.39)
Total (95% CI)	781	146		100.00	3.34 (2.30-4.86)

Total events: 476 (KIT group), 47 (WT group)
Test for heterogeneity: $\chi^2 = 10.10$, $df = 4$ ($P = 0.04$); $I^2 = 60.4\%$
Test for overall effect: $Z = 6.31$ ($P < 0.00001$)

0.1 0.2 0.5 1 2 5 10
KIT group WT group

B

Review:	Efficacy evaluation of imatinib therapy in patients with gastrointestinal stromal tumors: A meta-analysis				
Comparison:	02 KIT exon 11 group *vs* KIT exon 9 group				
Outcome:	01 cumulative response to imatinib				

Study or sub-category	KIT exon 11 group *n/N*	KIT exon 9 group *n/N*	OR (fixed) 95% CI	Weight (%)	OR (fixed) 95% CI
Debiec-Rychter *et al*[14] 2006	168/248	20/58		43.01	3.99 (2.18-7.29)
Wardelmann *et al*[15] 2006	10/22	4/7		13.61	0.63 (0.11-3.48)
Yeh *et al*[16] 2007	23/40	2/9		5.71	4.74 (0.87-25.71)
Rutkowski *et al*[17] 2007	42/52	4/9		5.39	5.25 (1.19-23.17)
Heinrich *et al*[18] 2008	180/283	12/32		32.28	2.91 (1.37-6.20)
Total (95% CI)	645	115		100.00	3.29 (2.17-5.00)

Total events: 423 (KIT exon 11 group), 42 (KIT exon 9 group)
Test for heterogeneity: $\chi^2 = 4.65$, $df = 4$ ($P = 0.33$); $I^2 = 13.9\%$
Test for overall effect: $Z = 5.60$ ($P < 0.00001$)

0.1 0.2 0.5 1 2 5 10
KIT exon 11 group KIT exon 9 group

C

Review:	Efficacy evaluation of imatinib therapy in patients with gastrointestinal stromal tumors: A meta-analysis				
Comparison:	03 KIT exon 9 group *vs* WT group				
Outcome:	01 cumulative response to imatinib				

Study or sub-category	KIT exon 9 group *n/N*	WT group *n/N*	OR (fixed) 95% CI	Weight (%)	OR (fixed) 95% CI
Debiec-Rychter *et al*[14] 2006	20/58	12/52		34.01	1.75 (0.76-4.07)
Wardelmann *et al*[15] 2006	4/7	2/3		4.92	0.67 (0.04-11.29)
Yeh *et al*[16] 2007	2/9	3/5		12.31	0.19 (0.02-2.06)
Rutkowski *et al*[17] 2007	4/9	5/19		7.33	2.24 (0.42-11.84)
Heinrich *et al*[18] 2008	12/32	25/67		41.44	1.01 (0.42-2.41)
Total (95% CI)	115	146		100.00	1.23 (0.73-2.10)

Total events: 42 (KIT exon 9 group), 47 (WT group)
Test for heterogeneity: $\chi^2 = 3.92$, $df = 4$ ($P = 0.42$); $I^2 = 0\%$
Test for overall effect: $Z = 0.78$ ($P = 0.44$)

0.1 0.2 0.5 1 2 5 10
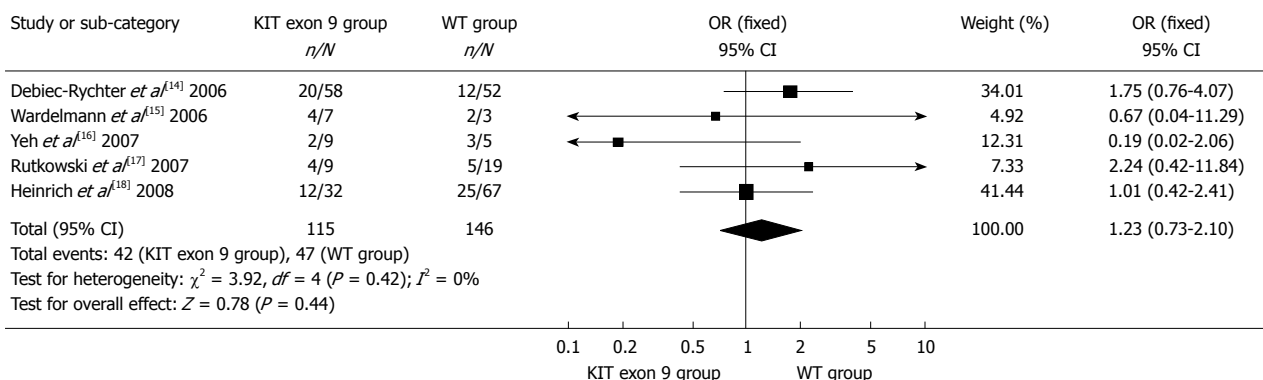KIT exon 9 group WT group

Figure 1 Meta-analysis. A: KIT group *vs* wide type (WT) group; B: KIT exon 11 group *vs* KIT exon 9 group; C: KIT exon 9 group *vs* WT group. OR: Odds ratios.

Publication bias

Begg's funnel plot was performed to access the publication bias of literatures. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 2A-C).

DISCUSSION

Before the introduction of imatinib mesylate (formerly known as STI571), poor responses to radiotherapy and chemotherapy made surgery the only realistic treatment to cure GIST[19-21].

Molecularly targeted therapy with imatinib can inhibit the etiologic aberrant cell signaling mechanisms in GIST, leading to major objective responses and prolonged disease control. Patients experienced a dramatic response, supporting the rational use of imatinib in this disease.

Table 1 Main characteristics of all studies included in the meta-analysis

Author	Dose distribution	Cumulative response (%)	Genotype	n			
				KIT	Exon 11	Exon 9	WT
Debiec-Rychter *et al*[14], 2006	400 mg/800 mg	56	Exon 11, 9, 13, 17 WT	315	248	58	52
Wardelmann *et al*[15], 2006	NA	50	Exon 11, 9 WT	29	22	7	3
Yeh *et al*[16], 2007	400 mg	52	Exon 11, 9 WT	49	40	9	5
Rutkowski *et al*[17], 2007	400 mg/800 mg	63	Exon 11, 9, 13, 17 WT	63	52	9	19
Heinrich *et al*[18], 2008	400 mg/800 mg	56	Exon 11, 9, 8, 13, 17 WT	325	283	32	67

WT: Wide type; NA: Not available.
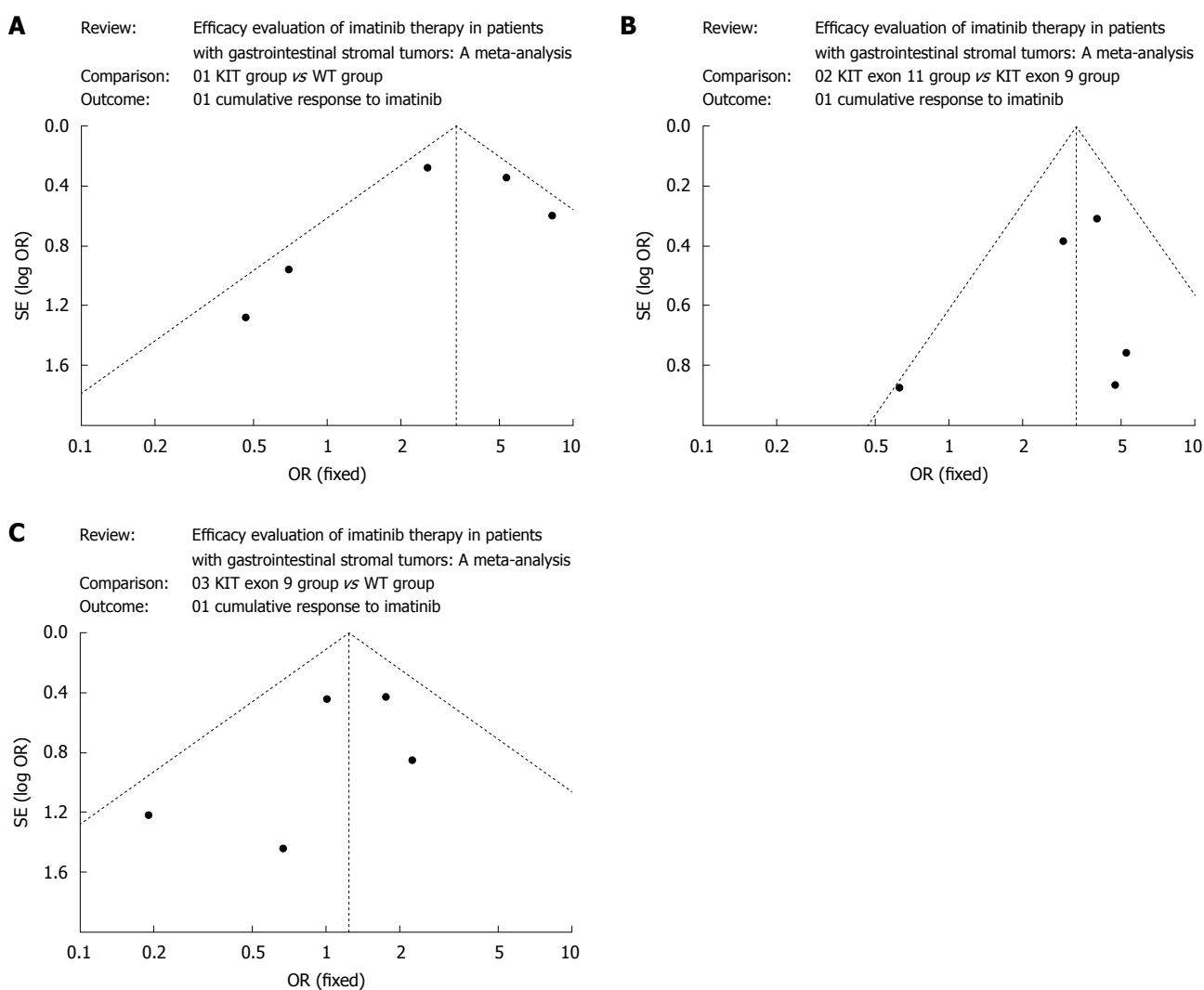
Figure 2 Begg's funnel plot for publication bias test. A: KIT group *vs* wide type (WT) group; B: KIT exon 11 group *vs* KIT exon 9 group; C: KIT exon 9 group *vs* WT group. OR: Odds ratios.

Prior studies have noted that imatinib can be effectively and safely administered. Imatinib has, therefore, become the standard of care in patients with advanced GIST. However, the secondary resistance to imatinib often occurs within the first or second year of treatment, which indicated the need for differential treatment proto-col for patients with GIST. According to previous reports, laboratory studies revealed significant molecular heterogeneity among GIST. Notably, 75%-85% of GIST had an activating mutation of KIT, 5%-7% had an activating mutation of the homologous PDGFRA kinase, and approximately 12%-15% of GIST did not have a detectable

mutation of either kinase. Mutations in KIT exon 11 were the most common imatinib-target mutation found among the confirmed and unconfirmed CD117-positive GISTs (71.3%), followed by mutations in KIT exon 9 (8.2%), KIT exon 13 (1.2%), PDGFRA exon 18 (1.2%), and KIT exon 17 (approximately 1%)[18]. Several studies have been designed to test the sensitivity of different genotypes of GIST to imatinib. Therefore, we made a meta-analysis of response to imatinib at different genotypes to identify which one is more sensitive to imatinib.

Objective tumor response was defined according to the Response Evaluation Criteria in Solid Tumors (RE-CIST)[22]. The best clinical response to imatinib was classified as cumulative response (CR) including complete response and partial response, stable disease, progressive disease, or not assessable. The conclusion shows that KIT mutation genotype correlates with improved treatment outcome when compared with WT genotype for cumulative response. Furthermore, patients whose tumor had a KIT exon 11 mutation were significantly more likely to achieve a CR than patients with tumors having a KIT exon 9 mutation, or WT genotype. There was no statistically significant difference in the likelihood of achieving a CR for patients with KIT exon 9-mutant GIST compared with WT GIST. Our findings confirmed that KIT exon 11 mutation is a positive predictive factor for cumulative response.

According to some phase III trials that were designed to compare 400 mg and 800 mg daily doses of imatinib, 400 mg remains the standard starting dose[23,24]. The survival of the patients with exon 9-mutant, exon 11-mutant or WT GIST was not affected by imatinib dosage. However, there was evidence of improved response rates for patients with exon 9-mutant tumors treated with imatinib 800 mg *vs* 400 mg (complete response/partial response, 67% *vs* 17%, $P = 0.02$)[16]. Remarkably, patients with tumors expressing an exon 9 mutant KIT protein show significant imatinib dose dependency for CR as compared with patients with tumors harbouring mutant exon 11 or wild-type KIT isoforms. These results suggest that 400 mg imatinib should be administered twice a day to patients with tumors bearing KIT exon 9 mutations. Other patients could safely start at an initial imatinib dose of 400 mg once daily, and increase to 800 mg when there is evidence of disease progression.

It appears that the WT expression of KIT is not sufficient to confer the antitumor activity of imatinib mesylate. Thus, inhibiting a normal target may not have antitumor activity if the target does not provide an essential function to the tumor cell. Therefore, identification of molecular abnormalities that are essential for tumorigenesis will help develop new anticancer therapies.

COMMENTS

Background
Gastrointestinal stromal tumor (GIST) commonly shows oncogenic activating mutations of the KIT tyrosine kinase. Imatinib mesylate, a small-molecule inhibitor of BCR-ABL, KIT and PDGFR tyrosine kinases, targets the aberrant signaling pathways that are critical for tumor cell proliferation and survival. Recent advances in understanding the molecular pathogenesis of GIST has led to the remarkably successful use of imatinib in the treatment of advanced tumors, inducing high response rates resulting in unprecedented improvement in the overall survival of the patients. Although several studies reported clinical response to imatinib with the mutational status to explore if the response to imatinib is linked to tumor genotype, a small sample can not provide persuasive evidence.

Research frontiers
Several studies with limited samples have concluded that clinical response to imatinib may correlate with mutational status. It is essential to give a personalized treatment by genotypes so as to improve the effectiveness in clinical treatment of GIST.

Innovations and breakthroughs
In the previous studies, it was found that the reason why a small sample size could not supply remarkable evidence to prove the response to imatinib may be linked to tumor genotype. The statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings. Meta-analysis is a statistical technique for assembling the results of several studies in a review into a single numerical estimate so as to provide a best evidence in making decisions about the treatment of individual patients.

Applications
The results indicate that most patients with different genotypes of GIST and KIT exon 11 mutant will benefit from the personalized treatment of imatinib.

Peer review
In this report, Chen *et al* performed a meta-analysis to confirm the prognostic importance of KIT mutation exon location with respect to imatinib sensitivity. Although this work does not add new information beyond what is already known, it is confirmatory and potentially useful for other investigators in this field.

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